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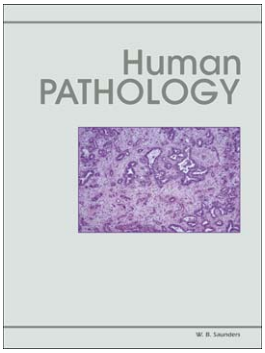

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Sean R Williamson MD, Ramya Gadde MD, Kiril Trpkov MD, Michelle S. Hirsch MD, PhD, John R Srigley MD, Victor E Reuter MD, Liang Cheng MD, L Priya Kunju MD, Ravi Barod MD, Craig G Rogers MD, Brett Delahunt MD, Ondrej Hes MD, John N Eble MD, Ming Zhou MD, PhD, Jesse K McKenney MD, Guido Martignoni MD, Stewart Fleming MD, David J Grignon MD, Holger Moch MD, Nilesh S Gupta MD

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Diagnostic Criteria for Oncocytic Renal Neoplasms: A Survey of Urologic Pathologists

Sean R Williamson, MD[1,2,3] Ramya Gadde, MD[1] Kiril Trpkov, MD[4] Michelle S. Hirsch, MD, PhD,[5] John R Srigley, MD[6] Victor E Reuter, MD[7] Liang Cheng, MD[8] L Priya Kunju, MD[9] Ravi Barod, MD[10] Craig G Rogers, MD[10] Brett Delahunt, MD[11] Ondrej Hes, MD[12] John N Eble, MD[8] Ming Zhou, MD, PhD[13] Jesse K McKenney, MD[14] Guido Martignoni, MD[15,16] Stewart Fleming, MD[17] David J Grignon, MD[8] Holger Moch, MD[18] Nilesh S Gupta, MD[1,2]

[1]Department of Pathology and Laboratory Medicine and [2]Henry Ford Cancer Institute, Henry Ford Health System, Detroit, MI, United States; [3]Department of Pathology, Wayne State University School of Medicine, Detroit, MI, United States; [4] Department of Pathology and Laboratory Medicine, Calgary Laboratory Service and University of Calgary, Calgary, AB, Canada; [5]Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States; [6]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; [7]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States; [8] Department of Pathology and Laboratory Medicine, Indiana University, Indianapolis, IN, United States; [9]Department of Pathology, University of Michigan School of Medicine, Ann Arbor, MI, United States; [10]Vattikutti Urology Institute, Henry Ford Health System, Detroit, MI, USA; [11]Department of Pathology and Molecular Medicine, Wellington School of Medicine and Health Sciences, University of Otago – Wellington,

Wellington, New Zealand; [12]Department of Pathology, Charles University in Prague, Faculty of Medicine in Plzeň, Pilsen, Czech Republic; [13]Department of Pathology, New York University Medical Center, New York, NY, United States; [14]Robert J. Tomsich Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH, USA; [15]Department of Pathology and Diagnostics, University of Verona, Verona, Italy; [16]Department of Pathology, Pederzoli Hospital, Peschiera del Garda, Italy; [17]Department of Cellular and Molecular Pathology, University of Dundee, Ninewells Hospital, Dundee, United Kingdom; [18]Department of Pathology, University Hospital Zurich, Zurich, Switzerland

Address correspondence and reprint requests to:
Sean R. Williamson, MD
Henry Ford Hospital, Department of Pathology - K6
2799 West Grand Blvd
Detroit, MI 48202
Email: seanwill@temple.edu
Phone: 313-916-3986
Fax: 313-916-2385

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ABSTRACT

Renal oncocytoma and chromophobe renal cell carcinoma (RCC) have been long recognized as distinct tumors; however, it remains unknown if uniform diagnostic criteria are used to distinguish these tumor types in practice. A survey was distributed to urologic pathologists regarding oncocytic tumors. Responses were received from 17/26 invitees. Histologically, >1 mitotic figure was regarded as most worrisome (n=10) or incompatible (n=6) with oncocytoma diagnosis. Interpretation of focal nuclear wrinkling, focal perinuclear clearing, and multinucleation depended on extent and did not necessarily exclude oncocytoma if minor. Staining techniques most commonly used included: CK7 (94%), KIT (71%), vimentin (65%), colloidal iron (59%), CD10 (53%), and AMACR (41%). Rare CK7-positive cells (≤5%) was regarded as most supportive of oncocytoma, although an extent excluding oncocytoma was not universal. Multiple chromosomal losses were most strongly supportive for chromophobe RCC diagnosis (65%). Less certainty was reported for chromosomal gain or a single loss. For tumors with mixed or inconclusive features, many participants use an intermediate diagnostic category (82%) that does not label the tumor as unequivocally benign or malignant, typically "oncocytic neoplasm" or "tumor" with comment. The term “hybrid tumor” was used variably in several scenarios. A slight majority (65%) report outright diagnosis of oncocytoma in needle biopsies. The morphologic, immunohistochemical, and genetic characteristics that define oncocytic renal tumors remain incompletely understood. Further studies correlating genetics, behavior, and histology are needed to define which tumors truly warrant classification as carcinomas for patient counseling and follow-up strategies.

Key words: Oncocytoma; chromophobe renal cell carcinoma; tumor classification; diagnostic criteria; immunohistochemistry; hybrid tumor

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INTRODUCTION

Renal oncocytoma[1] and chromophobe renal cell carcinoma[2,3] have been recognized for decades as unique renal tumor histologic subtypes, the former widely accepted as a benign neoplasm[4] and the latter largely considered a favorable renal cancer histology.[5] For the classic appearance of chromophobe renal cell carcinoma, there is little similarity to oncocytoma; however, it is well known that the eosinophilic variant[3] may cause a diagnostic challenge in distinguishing it from oncocytoma. Despite the fact that numerous techniques for differentiating these two tumor histologies have been explored over the years, including histochemical stains, immunohistochemistry, chromosomal changes, molecular assays, and electron microscopy,[6] it remains unknown if uniform diagnostic criteria are used by urologic pathologists in practice.

MATERIALS AND METHODS

An online survey (SurveyMonkey.com, Palo Alto, CA, USA) was written by 5 of the authors (SRW, RG, RB, CGR, and NSG). Twenty-six urologic pathologists were invited to participate in the survey, based on 1) the perception by the survey authors of the invitees as substantially interested in tumors of the kidney, and 2) in an attempt to obtain a broad geographic distribution of academic urologic pathologists. The survey consisted of 32 questions addressing histologic morphologic features, use of immunohistochemistry and other staining techniques, interpretation of molecular or chromosomal data, and reporting terminology, all of which are discussed as follows. Survey questions were based on text descriptions of histologic features and assay results (**Figure 1**), and therefore participants were not required to interpret images or stains. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of

Helsinki) for experiments involving humans. Informed consent was obtained from the participants in the form that the intended use of the data was explained, and participants were given the option to withdraw participation at any time including at the completion of the survey or afterward.

RESULTS

Seventeen participants completed the entire survey and were included in the dataset, including 2 of the survey authors (SRW and NSG). One invitee responded but declined to participate in the study, 1 survey response was incomplete (which was excluded), and no response was received from the remaining 7 invitees. Participants represented the United States (n=10), Canada (n=2), New Zealand (n=1), Czech Republic (n=1), Italy (n=1), United Kingdom (n=1), and Switzerland (n=1). Most participants (89%) confirmed evaluating >100 institutional renal tumors annually and many reported receiving personal consultation cases for opinion on renal tumors. Seven (41%) identified the kidney alone as their principle clinical or research interest, and the remainder reported the kidney in combination with one or more organs.

Histologic Features

Most participants responded that a few binucleated cells (82%) or multinucleated cells (71%) were compatible with a diagnosis of oncocytoma. For "frequent" binucleated cells or multinucleated cells, responses shifted to a larger fraction of participants considering these findings worrisome for carcinoma, but not necessarily incompatible with an oncocytoma diagnosis (**Figure 2**). Less certainty was reported for a small amount (making up <5% of the tumor) of nuclear wrinkling or perinuclear cytoplasmic clearing. Half of participants (53%) considered <5% extent of perinuclear clearing to be compatible

with an oncocytoma diagnosis and 41% responded similarly for minor nuclear wrinkling (**Figure 2**).

A majority considered identification of a single mitotic figure upon careful search to remain compatible with oncocytoma diagnosis (82%), whereas more than one was considered more uniformly worrisome (59%) or incompatible (35%) with oncocytoma diagnosis. Just over half (59%) considered a few intranuclear cytoplasmic invaginations (pseudoinclusions) to be compatible with an oncocytoma diagnosis; however, with increasing extent, this finding was reported as increasingly worrisome for malignancy (47%, **Figure 3**). Most respondents indicated that focal cytoplasmic clearing within areas of hyalinized stroma (central scar) was compatible with an oncocytoma diagnosis (82%), and similarly for a few papillary tufts protruding into cystic spaces (76%). A predominant solid, compact growth pattern or trabecular growth pattern (absence of separate round nests) were most commonly regarded as worrisome for carcinoma (53% and 59%, respectively).

Invasion of Structures

There was decreasing certainty for extension into structures as unequivocally compatible with an oncocytoma diagnosis, ranging from extension into perinephric fat[7-10] (59%) to involvement of renal sinus fat (53%) to invasion of the renal vein or a vein branch[7,11,12] (35%, **Figure 4**).

Special Staining and Immunohistochemistry

Respondents indicated they selectively use staining techniques in the differential diagnosis of oncocytoma, only when a specific differential diagnostic consideration is raised based on the histologic features (41%), usually in most cases (29%), in all cases

(24%, or combined 53% usually or always), and 6% rarely or never. The most commonly employed single antibody (94%) was cytokeratin 7 (CK7), although other commonly used techniques included KIT (71%), vimentin (65%), colloidal iron (Hale or modified Mowry methods, 59%), and CD10 (53%, **Figure 5**). Most participants (59%) reported that they perform succinate dehydrogenase (SDH) immunohistochemical staining only with unusual or borderline morphology (59%), or when morphology is highly suggestive of SDH-deficient renal cell carcinoma (29%).[13,14] None of the participants reported screening oncocytic tumors routinely for SDH status.

Staining Interpretation

Interpretation of staining results for CK7 is shown in Supplemental Tables 1-2 for diagnosis of oncocytoma (**Supplemental Table 1**) and chromophobe renal cell carcinoma (**Supplemental Table 2**). The largest majority of participants (82%) reported that CK7 positivity in <5% of tumor cells would be supportive of oncocytoma, whereas an entirely negative staining result was less uniformly considered supportive (59%) but still considered compatible (**Supplemental Table 1**). Interpretation shifted to worrisome or incompatible with oncocytoma as extent increased. For chromophobe renal cell carcinoma, diffuse CK7 positivity was endorsed uniformly as supportive of the diagnosis (100%), but there was less certainty reported for negative or focal staining (**Supplemental Table 2**). Colloidal iron interpretation is shown in **Supplemental Tables 3-4,** and vimentin interpretation is shown in **Supplemental Table 5**.

Genetic, Cytogenetic, and Molecular Assays

The largest fraction of respondents (41%) indicated that they have primarily used genetic, cytogenetic, or molecular assays for research purposes rather than clinical

diagnostics. Others reported using fluorescence in situ hybridization (FISH, 24%), conventional karyotyping (12%), or comparative genomic hybridization (6%) for diagnostic purposes. When interpreting genetic or cytogenetic changes, a majority (65%) endorsed losses of multiple chromosomes as supportive of chromophobe renal cell carcinoma diagnosis, whereas none (0%) reported that a single chromosomal loss was alone diagnostic of chromophobe renal cell carcinoma. Chromosomal gains were reported as supportive of chromophobe renal cell carcinoma diagnosis by 18%, whereas another 24% interpreted this as supportive of an alternative diagnosis, such as renal cell carcinoma unclassified, "hybrid" tumor, or other.

Borderline Cases

When encountering a borderline renal tumor with a combination of morphology, immunohistochemistry, or genetics that is not perfect for an unequivocal diagnosis of either oncocytoma or chromophobe renal cell carcinoma, 53% of participants reported using a borderline or intermediate diagnostic category with comment explaining the differential diagnosis (neither diagnosed as carcinoma nor benign). Another 24% reported diagnosing such cases as unclassified renal cell carcinoma. Another 18% would report a diagnosis favoring one of these diagnoses, and 6% would err for diagnosis of chromophobe renal cell carcinoma when features are not perfect for oncocytoma. When asked specifically, 82% confirmed using in clinical practice (for a resection specimen) an intermediate diagnostic category that does not unequivocally label the tumor as malignant, whereas 18% reported not using such a diagnosis. Such diagnoses almost uniformly included as a base "oncocytic renal [cell] neoplasm" with varying modifier terms, such as "low-grade", "borderline features", "unclassified", "low malignant potential", "uncertain

malignant potential", or "hybrid tumor". A slightly smaller percentage of participants would support creation of an official term for this scenario (76%).

When queried as to use of the diagnosis of "hybrid tumor" or "hybrid oncocytoma-chromophobe tumor", the most reported usage (41%) was when discrete areas of the tumor show typical features of oncocytoma and other areas show typical features of chromophobe renal cell carcinoma, regardless of whether a syndrome (such as Birt-Hogg-Dubé or renal oncocytosis) is known. Others reported using this term: never (18%); for any borderline tumor regardless of a syndrome (18%); only in the setting of a syndrome or apparent syndrome (12%); both in borderline cases and those with discrete areas of different morphology (6%); and rarely (6%) with a description of specific morphology provided.

Biopsy Diagnosis

A slight majority of participants would issue an outright diagnosis of oncocytoma in a needle biopsy specimen (64%). Of those that were unwilling to diagnose unequivocal oncocytoma in a biopsy sample (35%), diagnoses primarily were variations of "oncocytic neoplasm [or tumor], favor [or consistent with] oncocytoma".

Malignant Behavior of Oncocytoma-Like Neoplasms

Most participants (82%) reported never having encountered a tumor that closely mimicked an oncocytoma, yet which metastasized, whereas 3 (18%) reported encountering this scenario in a small number of cases over their careers.

DISCUSSION

Renal oncocytoma and chromophobe renal cell carcinoma are well recognized as distinctive renal cell tumors; however, challenges related to their pathologic diagnosis have

persisted since their recognition.[1-3] A wide array of biomarkers have been investigated for distinguishing these two tumor types;[6] however, how these are employed and interpreted in practice remains incompletely understood.[15] Although chromophobe renal cell carcinoma is generally accepted as an indolent form of renal cancer,[5] distinction from oncocytoma is not trivial, as it carries a potential psychological burden of a cancer diagnosis and healthcare costs and radiation exposure from surveillance.[16-19] This distinction also has implications for patient management, such as preoperative diagnosis via tumor biopsy[20-24] and imaging surveillance rather than resection.[25] Adjuvant therapy is currently not routinely employed after resection of localized renal cell carcinomas; however, enrollment in clinical trials may be dependent on this differential diagnosis, such as for oncocytic tumors with involvement of fat or blood vessels, for which the considerations would be between a benign tumor (oncocytoma) and high-stage (pT3a) renal cell carcinoma.

Regarding histologic features, the finding that emerged in this study as most worrisome for excluding an oncocytoma diagnosis was the presence of more than 1 identifiable mitotic figure, whereas 82% of participants felt that identification of a single mitotic figure upon careful search remained compatible with a diagnosis of oncocytoma (**Figure 3**). For other features characteristically associated with chromophobe renal cell carcinoma, such as binucleation, multinucleation, nuclear irregularities, perinuclear clearing, and intranuclear cytoplasmic invaginations, there was less certainty reported, and in general interpretation as compatible with oncocytoma diagnosis decreased with the extent of these features (**Figures 2 and 3**).

Several studies have reported that perinephric fat extension can occur with oncocytoma, without an apparent adverse effect on the benign behavior.[7-10] However, some concern persists regarding this finding, with only 59% of participants responding "compatible with oncocytoma diagnosis" and 41% considering it worrisome but not necessarily incompatible with oncocytoma. This decreased slightly to 53% for renal sinus fat involvement, which is well-known as an invasive pathway in clear cell renal cell carcinoma,[26] but has not been thoroughly studied in oncocytoma. A few studies have reported that vascular invasion, including renal vein invasion or renal vein branch invasion, does not necessarily alter the benign behavior of oncocytoma;[7,11,12] however, acceptance of this as compatible with oncocytoma decreased to 35%, with 41% considering it worrisome, and 24% considering it incompatible with a diagnosis of oncocytoma. We did not specifically assess whether the participants were aware of the literature supporting the benign behavior in this context or whether they felt the literature was not definitive; however, notably the largest study on this latter phenomenon [12] has only become published in the interim since the data for the current survey were already collected.

With regard to staining techniques, CK7 was reported as the most commonly used immunohistochemical antibody for oncocytoma diagnosis (94%). Surprisingly, the existing literature on this antibody demonstrates disparate results, with some studies reporting consistent positivity in oncocytoma and others reporting negative, or largely negative, results.[6] We suspect that this reflects threshold selection, as the vast majority of the tumor cells in oncocytoma are negative, with scattered positivity only in single cells and small clusters of cells.[15] If a binary reporting system is used, this could be interpreted as

either negative or positive, depending if a cutoff is used, or if any staining is defined as positive. The largest fraction of respondents (82%) interpreted focal staining of <5% of cells as supportive of oncocytoma. With increasing extent of CK7 positivity, interpretation in favor of oncocytoma decreased (**Supplemental Table 1**), although there was not agreement on an amount of positivity that excluded oncocytoma. For chromophobe renal cell carcinoma, diffuse CK7 positivity was endorsed as supportive of the diagnosis (100%), but there was less certainty reported for negative or focal staining (**Supplemental Table 2**). In general, negative colloidal iron staining was considered supportive of oncocytoma, and there was less certainty for partial staining patterns, such as an apical "bar" of staining[27] or other patterns (**Supplemental Table 3**).

Regarding chromosomal changes, oncocytomas often exhibit a diploid karyotype, loss of chromosome 1 or 14, or a few recurring rearrangements.[4] Conversely, chromophobe renal cell carcinoma is characterized by multiple losses of chromosomes, including 1, 2, 6, 10, 13, 17, 21, and Y.[5] The recent Cancer Genome Atlas analysis, however, noted that fewer such losses are found in eosinophilic variant chromophobe renal cell carcinoma.[28] Some studies have found that so-called "hybrid oncocytoma-chromophobe tumors" and the neoplasms of renal oncocytosis may have chromosomal gains as well as losses,[29,30] and similarly a combination of gains and losses has been also reported in usual chromophobe renal cell carcinoma.[31] As such we also queried the participants interpretation of chromosomal and genetic findings in this scenario. The greatest support was reported for multiple losses as supportive of chromophobe renal cell carcinoma (65%), whereas a single chromosome loss (excluding chromosome 1, since this is a shared finding with oncocytoma) was not considered inherently diagnostic of

chromophobe alone. There was no clear consensus for interpretation of chromosomal gains.

In cases with borderline features that are difficult to distinguish between oncocytoma and eosinophilic variant chromophobe renal cell carcinoma, a considerable majority of the urologic pathology specialists in this study were willing to use a borderline diagnostic category (82%) that does not label the tumor as unequivocally benign or malignant. Such diagnoses typically included as a base "oncocytic renal [cell] neoplasm" with varying modifier terms, such as "low-grade", "borderline features", "unclassified", "low malignant potential", "uncertain malignant potential", or "hybrid tumor". This study also revealed that there is some variability in the use of the term "hybrid tumor," or "hybrid oncocytoma-chromophobe tumor (HOCT)," which is used by pathologists in several scenarios: discrete mosaic or mixed morphology (41%), for any borderline tumor regardless of a syndrome (18%), only in the setting of a syndrome or apparent syndrome (12%), or never (18%). The current World Health Organization Classification discusses the occurrence of such "hybrid" tumors under the heading of chromophobe renal cell carcinoma;[32] however, it remains debated whether such tumors occurring with tumor syndromes and sporadically represent one or more distinct entities.[33]

Renal mass biopsy is increasingly important in clinical practice to guide management of renal tumors and to aid in consideration of various treatment options.[20-25] A slight majority of participants (64%) indicated willingness to diagnose oncocytoma outright by needle biopsy; however, those that do not (35%) typically diagnose "oncocytic neoplasm [or tumor], favor [or consistent with] oncocytoma". Regardless of the terminology used, clear communication and understanding between pathologists and

clinical colleagues is necessary to ensure appropriate management. As an example, some pathologists may use a diagnosis of unclassified renal cell carcinoma for an oncocytic tumor that cannot be categorized as either an oncocytoma or chromophobe renal cell carcinoma (24% in this survey). This approach reflects that the tumor that does not fit well into a defined category; however, a clear qualifier or discussion with clinicians would be warranted to convey that aggressive behavior is not suspected in light of the close resemblance to, and differential diagnosis with, oncocytoma and chromophobe renal cell carcinoma. Without such a qualifier or discussion, there may be a perception that unclassified renal cell carcinoma is highly aggressive,[34,35] which may be relevant to the role of adjuvant therapy in clinical trials. In contradistinction, despite that the academic uropathologists surveyed in this study reported evaluating a relatively large number of renal tumors, very few reported ever encountering a tumor that closely resembled oncocytoma that metastasized, which is mirrored by the lack of well-documented cases in the recent literature.

Limitations of the current survey are that it only queries the current state of this challenging area of diagnostics rather than establishing definitive guidelines. Of course, is not appropriate to define diagnostic criteria based purely on consensus opinion, in the absence of outcome data. Unfortunately, it may be challenging to collect an adequate number of metastatic oncocytic renal tumors, even interinstitutionally. It is also a limitation that only 17 of 26 invitees ultimately participated in the study, such that a considerable fraction (35%) of urologic pathologists perceived as interested in renal tumors were not sampled.

As there remains some variability and uncertainty in what defines oncocytoma, additional studies correlating genetics, outcome, and histology are needed to define which tumors truly warrant classification as carcinomas for patient counseling and follow-up strategies, especially now, entering the era of genomics and personalized medicine. The results of this study may nonetheless be helpful to general surgical pathologists in highlighting the potential use of a borderline category for some renal oncocytic tumors, and illustrating the few staining techniques that are most regularly employed by urologic pathologists in this scenario.

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Figure Legends:

Figure 1: Examples of challenging diagnostic features of oncocytic renal cell neoplasms: (A) In this core needle biopsy of an oncocytic renal tumor (20× magnification, hematoxylin and eosin), the cells have voluminous cytoplasm and a lower nuclear-cytoplasmic ratio, resembling chromophobe renal cell carcinoma; however, immunohistochemical staining characteristics were similar to those of oncocytoma, including minimal cytokeratin 7 labeling (not pictured). (B) In this core needle biopsy (10× magnification, hematoxylin and eosin), tumor cell cytology resembles that of oncocytoma; however, there is a trabecular rather than nested appearance. (C) This tumor diagnosed as oncocytoma demonstrates perinephric fat extension (10× magnification, hematoxylin and eosin). (D) This tumor was interpreted as oncocytoma, but it extends into the lumen of a large vein, with a thin vein wall at left and only an endothelial layer surrounding the tumor cells (10× magnification, hematoxylin and eosin). (E) This oncocytic neoplasm contains cells with uniform round nuclei (40× magnification, hematoxylin and eosin); however, there are scattered binucleated cells and there is minor perinuclear clearing ("halo"). (F) The same tumor demonstrates diffuse labeling for cytokeratin 7 (10× magnification, anti-cytokeratin 7 immunohistochemistry).

Figure 2: Survey responses for histologic features in relation to diagnosis of oncocytoma.

Figure 3: Survey responses for histologic features in relation to diagnosis of oncocytoma.

Figure 4: Survey responses for invasion of perinephric fat, renal sinus fat, and vein invasion in relation to diagnosis of oncocytoma

Figure 5: Staining techniques used by the survey participants in differential diagnosis of oncocytic renal tumors.

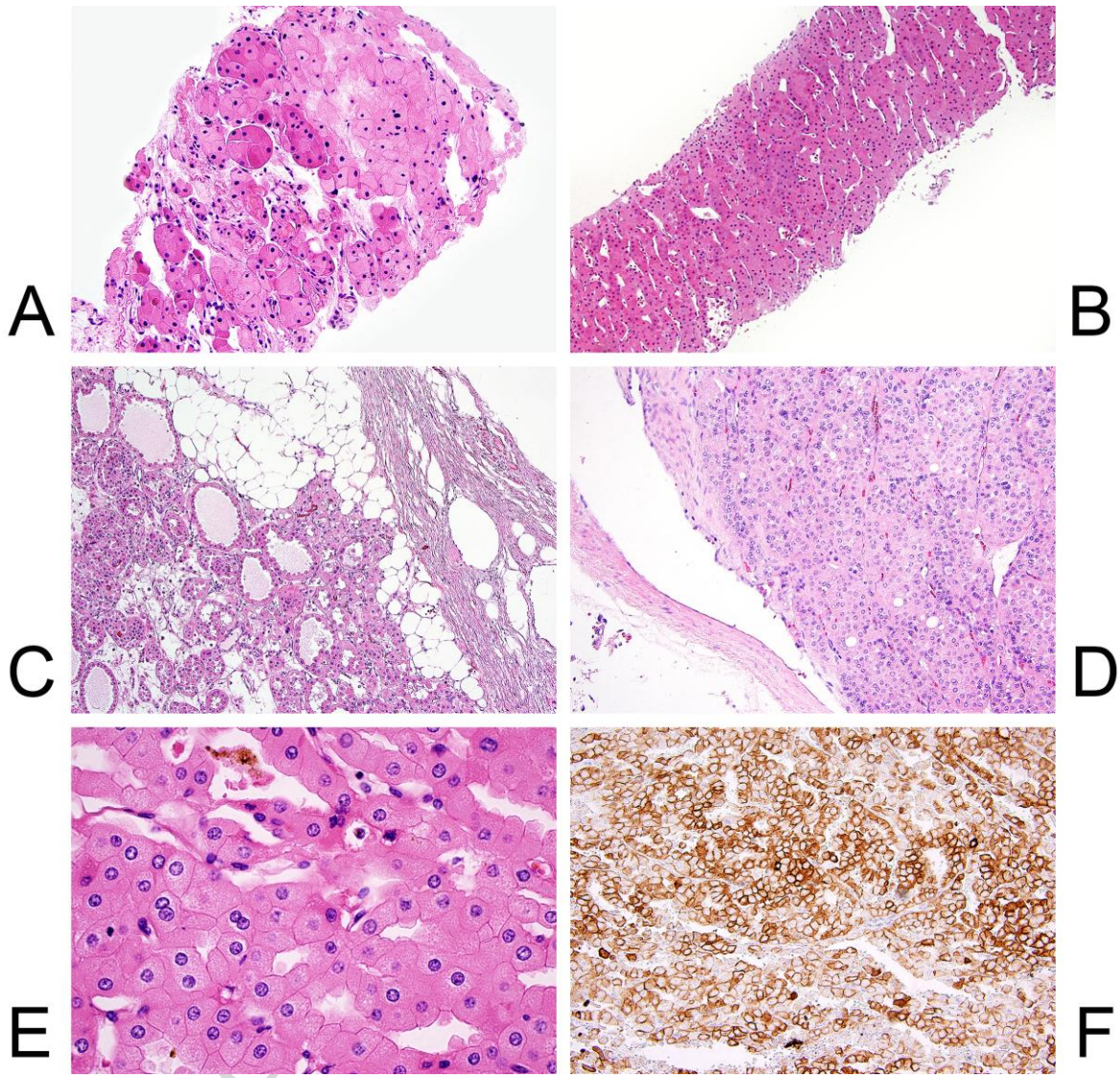

Figure 1

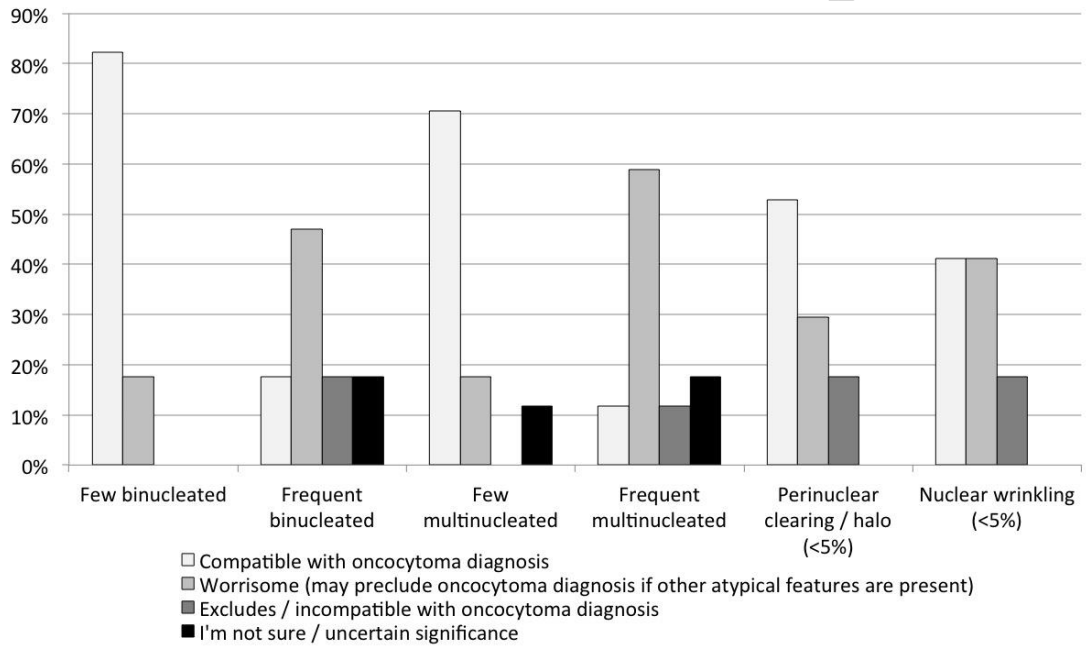

Figure 2

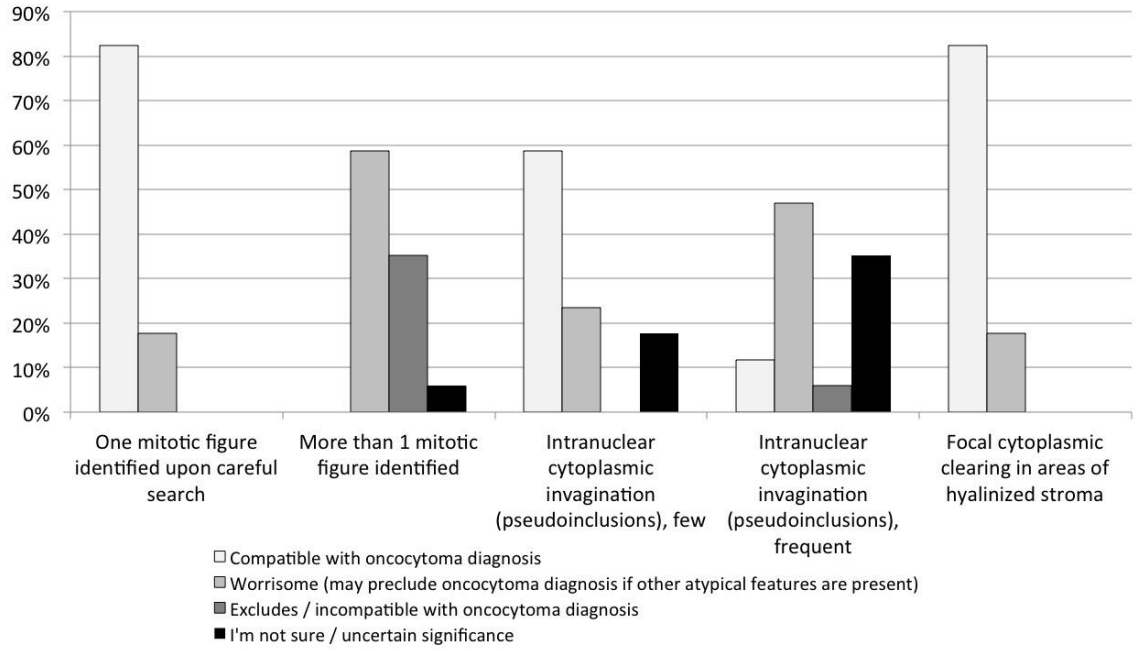

Figure 3

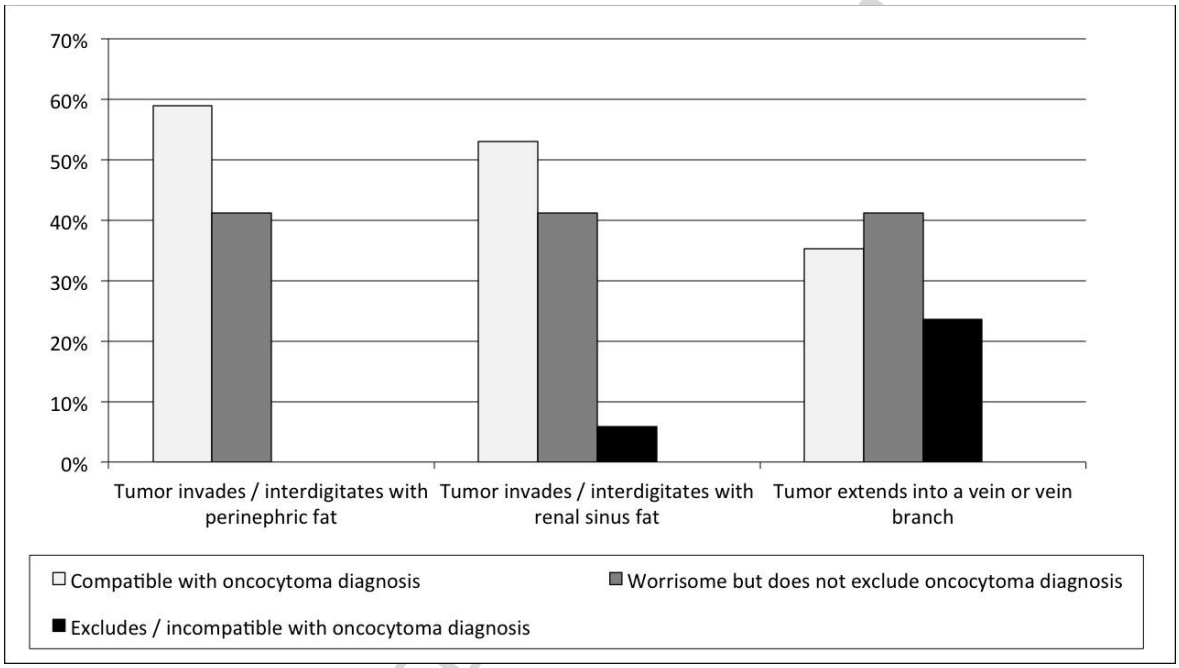

Figure 4

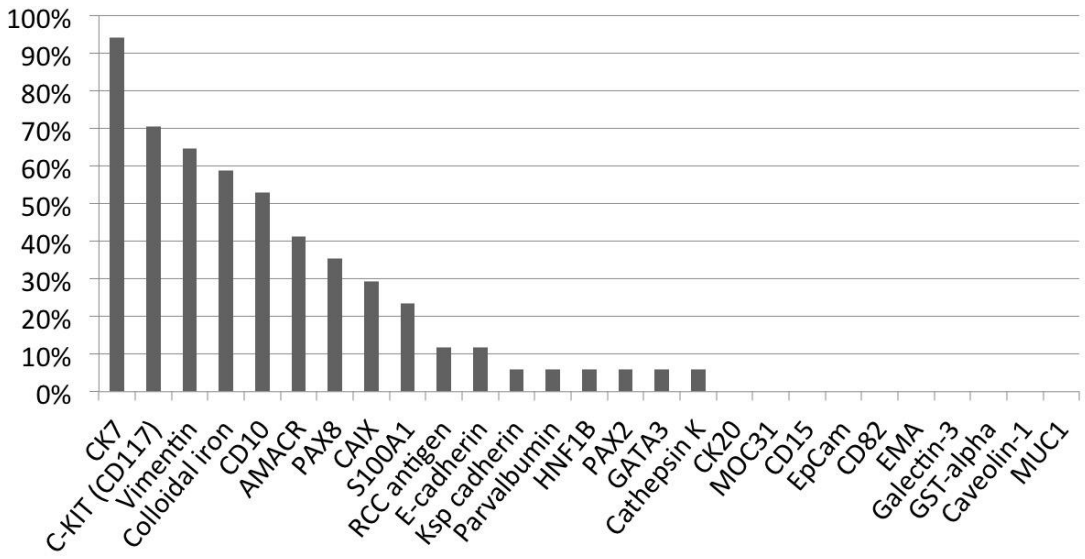

Figure 5